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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 31/4985, A61P 9/08, 15/10 | **A1**

(11) International Publication Number: **WO 00/15228**

(43) International Publication Date: 23 March 2000 (23.03.00)

(21) International Application Number: PCT/US99/19466

(22) International Filing Date: 26 August 1999 (26.08.99)

(30) Priority Data:
09/154,051 16 September 1998 (16.09.98) US

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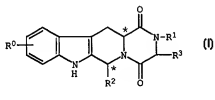
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMBINATIONS OF TETRACYCLIC CYCLIC GMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS WITH FURTHER THERAPEUTIC AGENTS



(I)

(a)

(57) Abstract

A compound of formula (I) and salts and solvates thereof, in which: R^0 represents hydrogen, halogen, or C_{1-6}alkyl; R^1 represents hydrogen, C_{1-6}-alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl, or heteroarylC_{1-3}alkyl; R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring (a) attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring (A) is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated, and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and R^3 represents hydrogen or C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain. A compound of formula (I) is a potent and selective inhibitor of cyclic guanosine 3', 5'-monophosphate specific phosphodiesterase (cGMP specific PDE) having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

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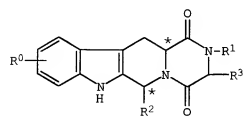
COMBINATIONS OF TETRACYCLIC CYCLIC GMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS WITH FURTHER THERAPEUTIC AGENTS

FIELD AND BACKGROUND OF THE INVENTION

This invention relates to a series of tetracyclic derivatives, to processes for their preparation, pharmaceutical compositions containing them, and to their use as therapeutic agents. In particular, the invention relates to tetracyclic derivatives that are potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP-specific PDE) having utility in a variety of therapeutic areas where such inhibition is thought to be beneficial, including the treatment of cardiovascular disorders and erectile dysfunction.

SUMMARY OF THE INVENTION

Thus, according to a first aspect, the present invention provides compounds of formula (I)



(I)

and salts and solvates (e.g., hydrates) thereof, in which:

R^0 represents hydrogen, halogen, or C_{1-6}alkyl;

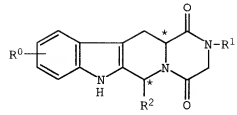
R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl, or heteroarylC_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen; and

R^3 represents hydrogen of C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain.

There is further provided by the present invention a subgroup of compounds for formula (I), the subgroup comprising compounds of formula (Ia)



(Ia)

and salts and solvates (e.g., hydrates) thereof, in which:

R^0 represents hydrogen, halogen, or C_{1-6}alkyl;

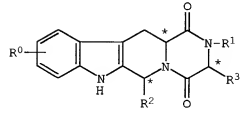
R^1 represents hydrogen, C_{1-6}alkyl, haloC_{1-6}-alkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl, or heteroarylC_{1-3}alkyl; and

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or an optionally substituted bicyclic ring

attached to the rest of the molecule via one of the benzene ring carbon atoms, and wherein the fused ring A is a 5- or 6-membered ring which can be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur, and nitrogen.

There is yet further provided by the present invention a further subgroup of compounds of

formula (I), the compounds comprising compounds of formula (Ib)



(Ib)

and solvates (e.g., hydrates) thereof, in which:

R^0 represents hydrogen, halogen, or C_{1-6}-alkyl;

R^1 represents hydrogen or C_{1-6}alkyl;

R^2 represents the bicyclic ring

or

which can be optionally substituted by one or more groups selected from halogen and C_{1-3}alkyl; and

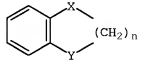
R^3 represents hydrogen or C_{1-3}alkyl.

Within R^1 above, the term "aryl" as part of an arylC_{1-3}alkyl group means phenyl or phenyl substituted by one or more (e.g., 1, 2, or 3) substituents selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and methylenedioxy. The term "heteroaryl" as part of a heteroarylC_{1-3}alkyl group means thienyl, furyl, or pyridyl, each optionally substituted by one or more (e.g., 1, 2, or 3) substituents selected from halo-

gen, C_{1-6}alkyl, and C_{1-6}alkoxy. The term "C_{3-8}cycloalkyl" as a group or part of a C_{3-8}cycloalkylC_{1-3}alkyl group means a monocyclic ring comprising three to eight carbon atoms. Examples of suitable cycloalkyl rings include the C_{3-6}cycloalkyl rings cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Within R^2 above, optional benzene ring substituents are selected from one or more (e.g., 1, 2, or 3) atoms or groups comprising halogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, CO_2R^b, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, cyano, nitro, and NR^aR^b, where R^a and R^b are each hydrogen or C_{1-6}alkyl, or R^a also can represent C_{2-7}alkanoyl or C_{1-6}alkylsulphonyl. Optional substituents for the remaining ring systems are selected from one or more (e.g., 1, 2, or 3) atoms or groups comprising halogen, C_{1-6}alkyl, C_{1-6}alkoxy, and arylC_{1-3}alkyl as defined above. The bicyclic ring

can, for example, represent naphthalene, a heterocycle such as benzoxazole, benzothiazole, benzisoxazole, benzimidazole, quinoline, indole, benzothiophene, benzofuran, or



wherein n is an integer 1 or 2 and X and Y each can represent CH_2, O, S, or NH.

In the above definitions, the term "alkyl," as a group or part of a group, means a straight chain or, where available, a branched chain moiety containing the indicated number of carbon atoms. For example, it can represent a C_{1-4}alkyl function as represented by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, and t-butyl. The term "alkenyl" as used herein includes straight chained and branched alkenyl groups containing the indicated number of carbon atoms, such as vinyl and allyl groups. The term "alkynyl" as used herein includes straight chained and branched alkynyl groups containing the indicated number of carbon atoms, suitably acetylene.

The term "halogen" herein means a fluorine, chlorine, bromine, or iodine atom.

The term "haloC_{1-6}alkyl" means an alkyl group as defined above comprising one to six carbon atoms substituted at one or more carbon atoms by one or more (e.g., 1, 2, or 3) halogen atoms. Similarly, a haloC_{1-6}alkoxy group is a haloC_{1-6}alkyl group as defined above linked to the R^2 benzene ring via an oxygen atom. Examples of haloC_{1-6}alkyl groups include trifluoromethyl and 2,2,2-trifluoroethyl. An example of a haloC_{1-6}alkoxy group is trifluoromethoxy. The term "C_{2-7}alkanoyl" means a C_{1-6}alkanoyl group where the C_{1-6}alkyl portion is as defined above. An example of a suitable C_{2-7}alkanoyl group is the C_2alkanoyl group acetyl.

When R^6 is a halogen atom or a C_{1-6}alkyl group, this substituent can be sited at any avail-

able position on the phenyl portion of the tetracyclic ring. However, a particular site of attachment is the ring 10-position.

The compounds of formula (I) can contain two or more asymmetric centers, and, thus, can exist as enantiomers or diastereoisomers. In particular, in formula (I) above, two ring chiral centers are denoted with asterisks. It is to be understood that the invention includes both mixture and separate individual isomers of the compounds of formula (I).

The compounds of formula (I) also can exist in tautomeric forms, and the invention includes both mixtures and separate individual tautomers thereof.

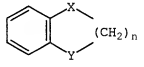
The pharmaceutically acceptable salts of the compounds of formula (I) which contain a basic center are acid addition salts formed with pharmaceutically acceptable acids. Examples include the hydrochloride, hydrobromide, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulphonate, and p-toluenesulphonate salts. Compounds of formula (I) also can provide pharmaceutically acceptable metal salts, in particular alkali metal salts, with bases. Examples include the sodium and potassium salts.

A particular group of compounds of the invention are those compounds of formula (I) in which R^0 is hydrogen or halogen (e.g., fluorine), especially hydrogen.

Another particular group of compounds of the invention are those compounds of formula (I) in which R^1 represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl,

C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, pyridylC_{1-3}alkyl, furylC_{1-3}alkyl, or optionally substituted benzyl. Within this particular group of compounds, examples of C_{1-4}alkyl groups are methyl, ethyl, n-propyl, i-propyl, and n-butyl. Examples of C_{3-6}cycloalkyl-methyl groups are cyclopropylmethyl and cyclohexyl-methyl. Examples of optionally substituted, benzyl groups include benzyl and halobenzyl (e.g., fluoro-benzyl).

A further group of compounds of the invention are those compounds of formula (I) in which R^2 represents an optionally substituted benzene, thiophene, furan, pyridine, or naphthalene ring, or an optionally substituted bicyclic ring



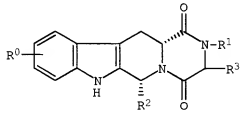
,

wherein n is 1 or 2, and X and Y are each CH_2 or O. Within this particular group of compounds, examples of substituted benzene groups are benzene substituted by one of halogen (e.g., chlorine), hydroxy, C_{1-3}alkyl (e.g., methyl, ethyl, or i-propyl), C_{1-3}-alkoxy (e.g., methoxy or ethoxy), CO_2R^b, halomethyl (e.g., trifluoromethyl), halomethoxy (e.g., trifluoromethoxy), cyano, nitro, or NR^aR^b wherein R^a and R^b are each hydrogen or methyl, or R^a is acetyl, or benzene substituted by dihalo (e.g., dichloro) or by C_{1-3}alkoxy (e.g., methoxy) and one of halogen (e.g., chlorine) and hydroxy. An example of a substituted

thiophene ring is a halo (e.g., bromo) substituted thiophene ring.

A still further particular group of compounds of formula (I) are those where R^3 represents hydrogen or R^1 and R^3 together represent a 3-membered alkyl chain.

A preferred group of compounds of the invention are the cis isomers of formula (I) represented by formula (Ic)



(Ic)

and mixtures thereof with their cis optical enantiomers, including racemic mixtures, and salts and solvates (e.g., hydrates) of these compounds in which R^0 is hydrogen or halogen (e.g., fluorine), especially hydrogen, and R^1, R^2, and R^3 are as defined previously.

The single isomers represented by formula (Ic), i.e., the 6R, 12aR isomers, are particularly preferred.

Within the above definitions, R^1 preferably can represent C_{1-4}alkyl (e.g., methyl, ethyl, i-propyl, and n-butyl), C_{3-6}cycloalkyl (e.g., cyclopentyl) or C_{3-6}cycloalkylmethyl (e.g., cyclopropylmethyl).

R^2 preferably can represent a substituted benzene ring such as benzene substituted by C_{1-3}-

alkoxy (e.g., methoxy) or by C_{1-3}alkoxy (e.g., methoxy) and halogen (e.g., chlorine), particularly 4-methoxyphenyl or 3-chloro-4-methoxyphenyl, or R^2 preferably can represent 3,4-methylenedioxyphenyl.

A particularly preferred subgroup of compounds according to the present invention are compounds wherein R^0 represents hydrogen.

A further preferred subgroup includes compounds wherein R^1 is selected from hydrogen, methyl, and isopropyl.

Preferably, R^2 represents the unsubstituted bicyclic ring

A still further subgroup of compounds of formula (I), are compounds wherein R^3 represents hydrogen or methyl.

It is to be understood that the present invention covers all appropriate combinations of particular and preferred groupings hereinabove.

Particular individual compounds of the invention include:

cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methylpyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':-6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo-[1",2":4'5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione;

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione;

(6R, 12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione; and physiologically acceptable solvates (e.g., hydrates) thereof.

Specific compounds of the invention are:

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione; and physiologically acceptable solvates (e.g., hydrates) thereof.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

It has been shown that compounds of the present invention are potent and selective inhibitors of cGMP-specific PDEs 1, 5, and 6, and particularly PDE5. Thus, compounds of formula (I) are of interest for use in therapy, specifically for the

treatment of a variety of conditions where selective inhibition of PDE5 is considered to be beneficial.

In summary, the biochemical, physiological, and clinical effects of PDE5 inhibitors suggest their utility in a variety of disease states in which modulation of smooth muscle, renal, hemostatic, inflammatory, and/or endocrine function is desirable. The compounds of formula (I), therefore, have utility in the treatment of a number of disorders, including stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, acute respiratory distress syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., postpercutaneous transluminal coronary or carotid angioplasty, or post-bypass surgery graft stenosis), peripheral vascular disease, vascular disorders, such as Raynaud's disease, thrombocythemia, inflammatory diseases, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, and diseases characterized by disorders of gut motility (e.g., irritable bowel syndrome).

An especially important use is the treatment of male erectile dysfunction, which is one form of impotence and is a common medical problem. Impotence can be defined as a lack of power, in the male, to copulate and can involve an inability to achieve penile erection or ejaculation, or both. The incidence of erectile dysfunction increases with age, with about 50% of men over the age of 40 suffering from some degree of erectile dysfunction.

Many compounds have been investigated for their therapeutic potential in the treatment of MED, including phenoxybenzamine, papaverine, prostaglandin E1 (PGE1), and phentolamine. These compounds, either alone or in combination, are typically self-administered by intracavernosal (i.c.) injection. While such treatments are effective, a treatment that is less invasive than injection therapy is preferred because pain, priapism, and fibrosis of the penis are associated with the i.c. administration of these agents.

For example, alprostadil (i.e., prostaglandin E1) delivered by intraurethral deposition has been approved for the treatment of MED. However, clinical studies showed that this route of administration is not effective in all patients. In addition, phentolamine and apomorphine are being evaluated as oral and sublingual therapies for MED, but neither compound has demonstrated efficacy across a broad range of subjects. Potassium channel openers (KCO) and vasoactive intestinal polypeptide (VIP) also have been shown to be active i.c., but cost and stability issues could limit development of the latter. An alternative to the i.c. route is the use of glyceryl trinitrate (GTN) patches applied to the penis, which has been shown to be effective but produces side effects in both patient and partner.

As an alternative to pharmacological treatment, a variety of penile prostheses have been used to assist achievement of an erection. The short-term success rate is good, but problems with infection and ischemia, especially in diabetic men,

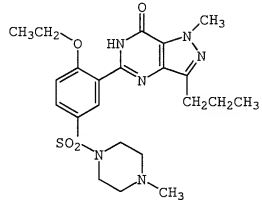
make this type of treatment a final option rather than a first-line therapy.

Because of the disadvantages of prior treatments for MED, new strategies to improve erectile response that exploit different physiological mechanisms are being investigated. One area of investigation is increasing the intracellular concentration of cGMP by providing a new type of oral therapy for the treatment of MED.

Increasing cGMP concentration is an important step in the physiology of penile erections. A penile erection is caused by neural stimuli that ultimately cause vasodilation of the arteries and sinusoidal spaces of the corpus cavernosum. Research indicates that nitric oxide plays a central role in this vasodilation.

In particular, atrial natriuretic peptides (ANP) and nitric oxide (NO, sometimes referred to as endothelium-derived relaxing factor or EDRF) relax smooth muscle by increasing guanylyl cyclase activity, which raises intracellular cGMP concentration. Intracellular cGMP is hydrolyzed by phosphodiesterases (PDEs), thereby terminating the action of the cyclic nucleotide. PDE5 is the major cGMP hydrolyzing enzyme in vascular smooth muscle. Accordingly, PDE5 inhibition potentiates the relaxant effects of ANP and nitric oxide by increasing the cGMP levels. Therefore, a compound that inhibits the PDE5 enzyme (and thereby indirectly inhibits the hydrolysis of cGMP) should potentiate the vascular response to nitric oxide, thereby facilitating the achievement and maintenance of erection.

PDE5 inhibitors have potential for use in treating male erectile dysfunction (MED), hypertension, heart failure, and other disease states because of their ability to facilitate the action of ANP and NO. For example, sildenafil, a PDE inhibitor showing little selectivity with respect to PDE6, has the structure:



and has shown efficacy in oral administration clinical trials for MED, which supports the hypothesis that augmenting normal or subnormal guanylyl cyclase stimuli has therapeutic benefits.

It is envisioned, therefore, that compounds of formula (I) are useful in the treatment of erectile dysfunction. Furthermore, the compounds can be administered orally, thereby obviating the disadvantages associated with intracavernosal administration. Thus, the present invention concerns the use of compounds of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition containing either entity, for the manu-

facture of a medicament for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man.

It also has been observed that human corpus cavernosum contains three distinct PDE enzymes (see A. Taher et al., *J. Urol., 149*, p. 285A (1993)), one of which is the cGMP-specific PDE5. As a consequence of the selective PDE5 inhibition exhibited by compounds of the present invention, the present compounds sustain cGMP levels, which in turn mediate relaxation of the corpus cavernosum tissue and consequent penile erection.

Although the compounds of the invention are envisioned primarily for the treatment of erectile dysfunction in humans, such as male erectile dysfunction and female sexual dysfunction, including orgasmic dysfunction related to clitoral disturbances, they also can be used for the treatment of premature labor and dysmenorrhea.

It is understood that references herein to treatment extend to prophylaxis, as well as treatment of established conditions.

It also is understood that "a compound of formula (I)," or a physiologically acceptable salt or solvate thereof, can be administered as the neat compound, or as a pharmaceutical composition containing either entity.

A further aspect of the present invention is providing a compound of formula (I) for use in the treatment of stable, unstable, and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, congestive heart failure, acute respiratory distress

syndrome, acute and chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency (e.g., post-PTCA or post-bypass graft stenosis), peripheral vascular disease, vascular disorders such as Raynaud's disease, thrombocythemia, inflammatory diseases, prophylaxis of myocardial infarction, prophylaxis of stroke, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, osteoporosis, preterm labor, benign prostatic hypertrophy, male and female erectile dysfunction, or diseases characterized by disorders of gut motility (e.g., IBS).

According to another aspect of the present invention, there is provided the use of a compound of formula (I) for the manufacture of a medicament for the treatment of the above-noted conditions and disorders.

In a further aspect, the present invention provides a method of treating the above-noted conditions and disorders in a human or nonhuman animal body which comprises administering to said body a therapeutically effective amount of a compound of formula (I).

Compounds of the invention can be administered by any suitable route, for example by oral, buccal, inhalation, sublingual, rectal, vaginal, transurethral, nasal, topical, percutaneous, i.e., transdermal, or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration. Parenteral administration can be accomplished using a needle and syringe, or using a high pressure technique, like POWDERJECT™. Oral administration generally is preferred.

With respect to treating sexual dysfunction and particularly erectile dysfunction in humans, oral administration of the compounds of the invention is the preferred route. Oral administration is the most convenient and avoids the disadvantages associated with intracavernosal administration. For patients suffering from a swallowing disorder or from impairment of drug absorption after oral administration, the drug can be administered parenterally, e.g., sublingually or buccally.

For administration to man in the curative or prophylactic treatment of the conditions and disorders identified above, oral dosages of a compound of formula (I) generally are about 0.5 to about 1000 mg daily for an average adult patient (70 kg). Thus, for a typical adult patient, individual tablets or capsules contain 0.2 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier, for administration in single or multiple doses, once or several times per day. Dosages for intravenous, buccal, or sublingual administration typically are 0.1 to 500 mg per single dose as required. In practice, the physician determines the actual dosing regimen which is most suitable for an individual patient, and the dosage varies with the age, weight, and response of the particular patient. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this invention.

For human use, a compound of the formula (I) can be administered alone, but generally is

administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compound can be administered orally, buccally, or sublingually in the form of tablets containing excipients such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents (e.g., methylcellulose, a semisynthetic glyceride such as witepsol, or mixtures of glycerides such as a mixture of apricot kernel oil and PEG-6 esters, or mixtures of PEG-8 and caprylic/capric glycerides). A compound also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, the compound is best used in the form of a sterile aqueous solution which can contain other substances, for example, salts, or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

For veterinary use, a compound of formula (I) or a nontoxic salt thereof, is administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen and route of administration that is most appropriate for a particular animal.

Thus, the invention provides in a further aspect a pharmaceutical composition comprising a

compound of the formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

There is further provided by the present invention a process of preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises mixing a compound of formula (I), together with a pharmaceutically acceptable diluent or carrier therefor.

In a particular embodiment, the invention includes a pharmaceutical composition for the curative or prophylactic treatment of erectile dysfunction in a male animal, including man, comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

A compound of formula (I) also can be used in combination with other therapeutic agents which can be useful in the treatment of the above-mentioned and other disease states. The invention thus provides, in another aspect, a combination of a compound of formula (I), together with a second therapeutically active agent.

A compound of formula (I) can be used in the preparation of a medicament for co-administration with the second therapeutically active agent in treatment of conditions where inhibition of a cGMP-specific PDE is beneficial. In addition, a compound of formula (I) can be used in the preparation of a medicament for use as adjunctive therapy with a second therapeutically active compound to treat such conditions. Appropriate doses of known second therapeutic agents for use in combination with a

compound of formula (I) are readily appreciated by those skilled in the art.

In particular, because compounds of the present invention maintain cGMP levels, the compounds of formula (I) can provide beneficial antiplatelet, antineutrophil, antivasospastic, vasodilatory, natriuretic, and diuretic activities, as well as potentiate the effects of endothelium-derived relaxing factor (EDRF), gastric NO administration, nitrovasodilators, atrial natriuretic factor (ANF), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and endothelium-dependent relaxing agents such as bradykinin, acetylcholine, and 5-HT_1.

The present selective PDE5 inhibitors in combination with vasodilators, including nitric oxide and nitric oxide donators and precursors, such as the organic nitrate vasodilators which act by releasing nitric oxide *in vivo*, are especially useful in treatment of angina, congestive heart failure, and malignant hypertension (e.g., pheochromocytoma). Related to the capacity of the present PDE5 inhibitors to potentiate nitric oxide donors and precursors is their ability, in spontaneously hypertensive rats, to reverse the desensitization to these agents that occurs with chronic use.

Examples of vasodilators that can be used in conjunction with the compounds of formula (I) include, but are not limited to, (a) organic nitrates, such as nitroglycerin, isosorbide dinitrate, pentaerythrityl tetranitrate, isosorbide-5-mononitrate, propatyl nitrate, trolnitrate, nicroandil, mannitol hexanitrate, inositol hexanitrate, N-[3-nitratopivaloyl]-L-cysteine ethyl ester, (b)

organic nitrites, like isoamyl nitrite, (c) thionitrites, (d) thionitrates, (e) S-nitrosothiols, like S-nitroso-N-acetyl-D,L-penicillamine, (f) nitrosoproteins, (g) substituted furoxanes, such as 1,2,5-oxadiazole-2-oxide and furazan-N-oxide, (h) substituted sydnonimines, such as molsidomine and mesocarb, (i) nitrosyl complex compounds, like iron nitrosyl compounds, especially sodium nitroprusside, and (j) nitric oxide (NO) itself.

Other classes of therapeutic agents that can be used in conjunction with the compounds of formula (I), in addition to vasodilators, include, but are not limited to, α-adrenergic blockers, mixed α,β-blockers, prostaglandin EI (PGEI) and prostacyclin (PGI2), angiotensin converting enzyme inhibitors (ACE inhibitors), neutral endopeptidase (NEP) inhibitors, centrally acting dopaminergic agents (such as apomorphine), vasoactive intestinal peptides (VIP), calcium channel blockers, and compounds like thiazides.

Alpha-adrenergic blockers inhibit vasoconstriction in the corpus cavernosum. Because PDE5 inhibitors enhance vasodilation of the same smooth muscle tissue, a PDE5 inhibitor of formula (I) and an α-adrenergic blocker, like phentolamine or prazocin, or a centrally acting dopaminergic agent, like apomorphine, can be expected to potentiate one another in a treatment for MED or other disorders. Potentiation of mixed α,β-blockers, like carvedilol, which is employed in treatment of hypertension, also is expected. Similarly, α_2-adrenergic blockers, like yohimbine, can be potentiated.

Prostaglandin E1 enhances relaxation of the corpus cavernosum by increasing the formation of cyclic AMP. Cyclic AMP can be degraded in the corpus cavernosum by PDE3, which is inhibited by cyclic GMP. By maintaining cyclic GMP levels, a PDE5 inhibitor can indirectly inhibit PDE3 activity, and hence block degradation of cyclic AMP. Therefore, a PDE5 inhibitor of formula (I) can be expected to potentiate the activity of PGE1 in the treatment of MED or compounds having similar activities, such as PGI2, in the treatment of pulmonary hypertension, for example.

Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I into angiotensin II, which causes systemic vasoconstriction and the retention of sodium and water. PDE5 inhibitors cause vasodilation in hypertensive animals, and stimulate the excretion of sodium and water in normotensive animals. Therefore, a PDE5 inhibitor of formula (I) can be combined with an ACE inhibitor to achieve more powerful vasodilatory and natriuretic effects in, for example, treatment of congestive heart failure or hypertensive states.

Neutral endopeptidase (NEP) inhibitors inhibit the degradation of atrial natriuretic peptide (ANP) by NEP. PDE5 inhibitors can be expected to potentiate the action of ANP by inhibiting degradation of its second messenger, cyclic GMP, and, therefore, a compound of formula (I) can potentiate the effects of agents, like NEP inhibitors, that increase blood levels of ANP.

The combination referred to above can be presented for use in the form of a single pharma-

ceutical formulation, and, thus, pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier comprise a further aspect of the invention.

The individual components of such a combination, therefore, can be administered either sequentially or simultaneously from the same or separate pharmaceutical formulations. As is the case for the PDE5 inhibitors of formula (I), a second therapeutic agent can be administered by any suitable route, for example, by oral, buccal, inhalation, sublingual, rectal, vaginal, trans-urethral, nasal, topical, percutaneous (i.e., trans-dermal), or parenteral (including intravenous, intramuscular, subcutaneous, and intracoronary) administration.

In some embodiments, the compound of formula (I) and the second therapeutic agent are administered by the same route, either from the same or from different pharmaceutical compositions. However, in other embodiments, using the same route of administration for the compound of formula (I) and the second therapeutic agent either is impossible or is not preferred. For example, if the second therapeutic agent is nitric oxide, which typically is administered by inhalation, the compound of formula (I) must be administered by a different route. Furthermore, if a compound of formula (I) is used in combination with a nitrate vasodilator, for example, in treatment of an erectile dysfunction, it is preferred that the compound of formula (I) is administered orally and

the vasodilator is administered topically, and preferably in a manner which avoids substantial systemic delivery of the nitrate.

The combination of a compound of formula (I) and a second therapeutic agent is envisioned in the treatment of several disease states. Examples of such treatments are the systemic and topical treatment of male and female sexual dysfunction, wherein a compound of formula (I) is used in combination with phentolamine, prazocin, apomorphine, PDE1, or a vasoactive intestinal peptide. The compound of formula (I) can be administered orally or transuretherally, and the second therapeutic agent can be administered orally, topically, or intracavernosally, for example. Persons skilled in the art are aware of the best modes of administration for each therapeutic agent, either alone or in a combination.

Other disease states that can be treated by a combination of a compound of formula (I) and a second therapeutic agent include, but are not limited to:

(a) treatment of hypertension using a compound of formula (I) in combination with an α-adrenergic blocker, a mixed α,β-blocker, like carvedilol, a thiazide, sodium nitroprusside, an ACE inhibitor, or a calcium channel blocker;

(b) treatment of pulmonary hypertension using a compound of formula (I) in combination with inhaled NO on other

inhaled vasodilators, or with PGI2 administered via an IV pump; and

(c) treatment of chronic obstructive pulmonary disease using a compound of formula (I) in combination with inhaled NO.

Examples of individual compounds of the invention for use in the treatment of erectile dysfunction include:

cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]furan-5-yl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-butyl-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(5aR, 12R, 14aS)-1,2,3,5,6,11,12,14a-octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo-[1",2":4',5']pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione;

cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione;

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and physiologically acceptable salts and solvates (e.g., hydrates) thereof.

Especially useful specific compounds of the invention are:

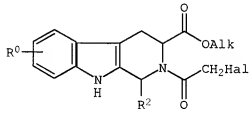
(6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and

(3S, 6R, 12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione; and physiologically acceptable salts and solvates (e.g., hydrates) thereof.

Compounds of formula (I) can be prepared by any suitable method known in the art or by the following processes which form part of the present invention. In the methods below, R^0, R^1, and R^2 are

as defined in formula (I) above unless otherwise indicated.

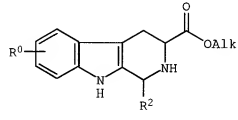
Thus, a process (A) for preparing a compound of formula (I) wherein R^3 represents hydrogen comprises treating a compound of formula (II)



(II)

in which Alk represents C_{1-6}alkyl, e.g., methyl or ethyl, and Hal is a halogen atom, e.g., chlorine, with a primary amine R^1NH_2 in a suitable solvent, such as an alcohol (e.g., methanol or ethanol) or a mixture of solvents, conveniently at a temperature of from 20°C to reflux (e.g., at about 50°C).

A compound of formula (II) can be conveniently prepared by treating a compound of formula (III)



(III)

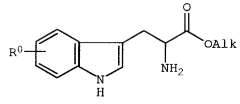
with a haloacetyl halide (e.g., chloroacetyl chloride) in a suitable solvent, such as a halogenated hydrocarbon (e.g., trichloromethane or dichloromethane) or an ether (e.g., tetrahydrofuran), preferably in the presence of a base such as an organic amine (e.g., a trialkylamine such as triethylamine) or an alkali metal carbonate or bicarbonate (e.g., $NaHCO_3$). The reaction conveniently can be effected at a temperature of from -20°C to +20°C (e.g., at about 0°C).

A compound of formula (I) also can be prepared from a compound of formula (III) in a two-step procedure via a compound of formula (II) isolated without purification.

Compounds of formula (I) can be prepared as individual enantiomers in two steps from the appropriate enantiomer of formula (III) or as mixtures (e.g., racemates) of either pairs of cis or trans isomers from the corresponding mixtures of either pairs of cis or trans isomers of formula (III).

Individual enantiomers of the compounds of the invention can be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for examples, using HPLC (high performance liquid chromatography) on a chiral column such as Hypersil naphthylurea.

A compound of formula (III) conveniently can be prepared from a tryptophan alkyl ester of formula (IV)



(IV)

(where Alk is as previously defined) or a salt thereof (e.g., the hydrochloride salt) according to either of the following procedures (a) and (b). Procedure (b) is only suitable for preparing cis isomers of formula (III) and can be particularly suitable for preparing individual cis enantiomers of formula (III) from D- or L- tryptophan alkyl esters as appropriate.

Procedure (a)

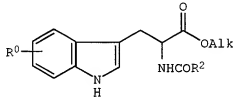
This comprises a Pictet-Spengler cyclization between a compound of formula (IV) and an aldehyde R^2CHO. The reaction can be conveniently effected in a suitable solvent such as a halogenated hydrocarbon (e.g., dichloromethane) or an aromatic hydrocarbon (e.g., toluene) in the presence of an acid, such as trifluoroacetic acid. The reaction conveniently can be carried out at a temperature of from -20°C to reflux to provide a compound of formula (III) in one step. The reaction also can be carried out in a solvent such as an aromatic hydrocarbon (e.g., benzene or toluene) under reflux, optionally using a Dean-Stark apparatus to trap the water produced.

The reaction provides a mixture of cis and trans isomers which can be either individual enantiomers or racemates of pairs of cis or trans isomers, depending upon whether racemic or enantiomerically pure tryptophan alkyl ester was used as the starting material. Individual cis or trans enantiomers conveniently can be separated from mixtures thereof by fractional crystallization or by chromatography (e.g., flash column chromatography) using appropriate solvents and eluents. Similarly, pairs of cis and trans isomers can be separated by chromatography (e.g., flash column chromatography) using appropriate eluents. An optically pure trans isomer also can be converted to an optically pure cis isomer using suitable epimerization procedures. One such procedure comprises treating the trans isomer or a mixture (e.g., 1:1 mixture) of cis and trans isomers with methanolic or aqueous hydrogen chloride at a temperature of from 0°C to the refluxing temperature of the solution. The mixture then can be subjected to chromatography (e.g., flash column chromatography) to separate the resulting diastereoisomers, or in the procedure utilizing aqueous hydrogen chloride, the desired cis isomer precipitates out as the hydrochloride salt which then can be isolated by filtration.

Procedure (b)

This comprises a four-step procedure from a compound of formula (IV) or a salt thereof (e.g., the hydrochloride salt). The procedure is particularly suitable for preparing a 1R, 3R isomer of

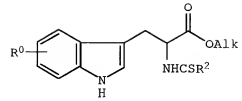
formula (III) from a D-tryptophan alkyl ester of formula (IV) or a salt thereof (e.g., the hydrochloride salt). Thus, a first step (i) comprises treating a compound of formula (IV) with an acid halide R^2COHal (where Hal is as previously defined) in the presence of a base, e.g., an organic base such as a trialkylamine (for example, triethylamine), to provide a compound of formula (V).



(V)

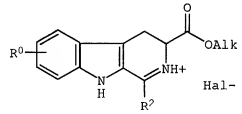
The reaction can be conveniently carried out in a suitable solvent, such as a halogenated hydrocarbon (e.g., dichloromethane) or an ether (e.g., tetrahydrofuran), and at a temperature of from -20°C to +40°C.

Step (ii) comprises treating a compound of formula (V) with an agent to convert the amide group to a thioamide group. Suitable sulfurating agents are well known in the art. Thus, for example, the reaction can be conveniently effected by treating (V) with Lawesson's reagent. This reaction can be conveniently carried out in a suitable solvent, such as ether (e.g., dimethoxyethane) or an aromatic hydrocarbon (e.g., toluene), at an elevated temperature, such as from 40°C to 80°C to provide a compound of formula (VI)



(VI)

Step (iii) comprises treating a compound of formula (VI) with a suitable agent to provide a compound of formula (VII)



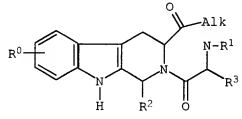
(VII)

wherein Hal is a halogen atom, e.g., iodine. The reaction can be conveniently effected by treating (VI) with an alkylating agent, such as a methyl halide (e.g., methyl iodide), or an acylating agent, such as an acetyl halide (e.g., acetyl chloride), in a suitable solvent, such as a halogenated hydrocarbon (e.g., dichloromethane) at an elevated temperature (e.g., under reflux).

In step (iv), the resulting iminium halide of formula (VII) can be treated with a reducing agent, such as a boron hydride, e.g., sodium borohydride, to provide the desired compound of formula (III). The reduction can be conveniently effected

at a low temperature, e.g., within the range of -100°C to 0°C, in a suitable solvent, such as an alcohol (e.g., methanol).

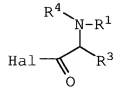
There is further provided by the present invention a process (B) for preparing a compound of formula (I), wherein R^1 and R^3 together represent a 3- or 4-membered alkyl or alkenyl chain, which process (B) comprises cyclization of a compound of formula (VIII)



(VIII) ,

wherein Alk represents C_{1-6}alkyl and R^1 and R^3 together represent a 3- or 4-membered chain, both as hereinbefore described. The cyclization is suitably carried out in an organic solvent or solvents, such as an alcoholic solvent (e.g., methanol), and optionally an ether solvent such as tetrahydrofuran, and in the presence of a reducing agent, aptly a palladium catalyst, such as palladium on carbon.

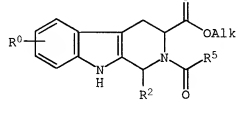
Conveniently, a compound of formula (VIII) is prepared by reaction of a compound of formula (III) as hereinbefore described with a compound of formula (IX)



(IX) ,

wherein Hal represents a halogen atom as hereinbefore described, R^1 and R^3 together represent a 3- or 4-membered chain as hereinbefore described, and R^4 represents a protecting group, suitably a benzyloxycarbonyl group or the like. Typically, the reaction is carried out in a chlorinated organic solvent, such as dichloromethane, and a tertiary amine, such as triethylamine or the like.

According to a further aspect of the present invention, there is provided a process (C) for preparing a compound of formula (I) wherein R^3 represents C_{1-3}alkyl, which process comprises cyclization of a compound of formula (X)



(X) ,

wherein Alk represents C_{1-6}alkyl as hereinbefore described and R^5 represents C_{2-5}alkyl, substituted at C_1 by a halogen atom, the halogen atom being as

hereinbefore described. Suitably, the cyclization is achieved by reflux for many hours, such as 22 to 26 hours, in the presence of an ether solvent, such as tetrahydrofuran, and a suitable amine as hereinafter described in the accompanying examples.

Aptly, a compound of formula (X) can be prepared from a compound of formula (III) by suitable acylation techniques, such as reaction with a C_{3-6}carboxylic acid, substituted at C-2 by a halogen atom in a halogenated organic solvent, such as dichloromethane.

Compounds of formula (I) can be converted to other compounds of formula (I). Thus, for example, when R^2 is a substituted benzene ring, it may be necessary or desirable to prepare the suitably substituted compound of formula (I) subsequent to process (A), (B), or (C), as above. Examples of appropriate interconversions include nitro to amino or aralkyloxy to hydroxy by suitable reducing means (e.g., using a reducing agent such as $SnCl_2$ or a palladium catalyst, such as palladium-on-carbon), or amino to substituted amino, such as acylamino or sulphonylamino using standard acylating or sulphonylating conditions. In the case where R^2 represents a substituted bicyclic system, suitable interconversion can involve removal of a substituent, such as by treatment with a palladium catalyst (e.g., palladium-on-carbon) whereby, for example, a benzyl substituent can be removed from a suitable bicyclic system.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I), which contain a basic center, can be treated with a

suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques.

Compounds of the invention can be isolated in association with solvent molecules by crystallization from or evaporation of an appropriate solvent.

Thus, according to a further aspect of the invention, we provide a process for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) thereof which comprises process (A), (B), or (C) as hereinbefore described followed by

(i) an interconversion step, and/or either

(ii) salt formation, or

(iii) solvate (e.g., hydrate) formation.

There is further provided by the present invention compounds of formulae (II), (VIII), (X), and further compounds of formulae (III), (V), (VI), and (VII), with the exception for compounds (III), (V), (VI), and (VII), wherein R^0 is hydrogen, R^2 is phenyl, and Alk is methyl.

The pharmaceutically acceptable acid addition salts of the compounds of formula (I) which contain a basic center can be prepared in a conventional manner. For example, a solution of the free base can be treated with a suitable acid, either

neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts can be obtained in an analogous manner by treating a solution of a compound of formula (I) with a suitable base. Both types of salt can be formed or interconverted using ion-exchange resin techniques.

Thus, according to a further aspect of the invention, a method for preparing a compound of formula (I) or a salt or solvate (e.g., hydrate) is provided, wherein the method comprises process (A), (B), or (C) as hereinbefore described, followed by (i) salt formation, or (ii) solvate (e.g., hydrate) formation. The method of preparing the following Intermediates 1 through 92 and Examples 1 through 125, and characterization of the compounds, can be found in published PCT applications WO 95/19978, WO 97/03985, and WO 97/03675, incorporated herein by reference.

Intermediates 1 and 2
Methyl 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 3 and 4
Methyl 1,2,3,4-tetrahydro-1-(4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 5
Methyl 1,2,3,4-tetrahydro-1-(3-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

Intermediates 6 and 7
Methyl 1,2,3,4-tetrahydro-1-(4-ethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 8 and 9
Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydrobenzo[b]-furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 10 and 11
Methyl 1,2,3,4-tetrahydro-1-(3,4-ethylenedioxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 12
Methyl 1,2,3,4-tetrahydro-1-(2-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

Intermediates 13 and 14
Methyl 1,2,3,4-tetrahydro-1-(4-chlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 15 and 16
Methyl 1,2,3,4-tetrahydro-1-(3,4-dichlorophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 17
Methyl 1,2,3,4-tetrahydro-1-(1,2,3,4-tetrahydro-6-naphthyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

Intermediates 18 and 19
Methyl 1,2,3,4-tetrahydro-1-(2-naphthyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 20 and 21
Methyl 1,2,3,4-tetrahydro-1-(2-thienyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 22 and 23
Ethyl 1,2,3,4-tetrahydro-1-(3-thienyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 24 and 25
Methyl 1,2,3,4-tetrahydro-1-(5-bromo-2-thienyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 26 and 27
Methyl 1,2,3,4-tetrahydro-1-(4-bromo-2-thienyl))-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 28
Methyl 1,2,3,4-tetrahydro-1-(3-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

Intermediates 29 and 30
Ethyl 1,2,3,4-tetrahydro-1-(5-methyl-2-furyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 31 and 32
Ethyl 1,2,3,4-tetrahydro-1-(4-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 33 and 34
Methyl 1,2,3,4-tetrahydro-1-(3-methylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 35 and 36
Methyl 1,2,3,4-tetrahydro-1-(4-trifluoromethyl-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 37 and 38
Ethyl 1,2,3,4-tetrahydro-1-(4-cyanophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 39
Methyl 1,2,3,4-tetrahydro-1-(4-hydroxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

Intermediate 40
Methyl 1,2,3,4-tetrahydro-1-(3-hydroxy-4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

Intermediate 41
Methyl 1,2,3,4-tetrahydro-1-(4-hydroxy-3-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer

Intermediate 42
Methyl 1,2,3,4-tetrahydro-1-(4-ethylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 43 and 44
Methyl 1,2,3,4-tetrahydro-1-(4-isopropylphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 45 and 46
Ethyl 1,2,3,4-tetrahydro-1-(4-nitrophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 47
Ethyl 1,2,3,4-tetrahydro-1-(4-dimethylaminophenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of cis and trans isomers

Intermediates 48 and 49
Ethyl 1,2,3,4-tetrahydro-1-(3-pyridyl)-9H-pyrido-[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 50 and 51
Methyl 1,2,3,4 tetrahydro-6-fluoro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 52 and 53
Methyl 1,2,3,4-tetrahydro-6-fluoro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 54 and 55
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 56
(1S, 3S) Methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1R, 3S) methyl-1,2,3,4-tetrahydro-1-(3,4-methylene-dioxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediates 57 and 58
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(4-methoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediates 59 and 60
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3-chloro-4-methoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediates 61 and 62
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(2,3-dihydro-benzo[b]furan-5-yl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-(2,3-dihydro-benzo[b]furan))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediates 63 and 64
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-indanyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 65
Ethyl 1,2,3,4-tetrahydro-1-(4-trifluoromethoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediate 66
Methyl 1,2,3,4-tetrahydro-1-(5-methyl-2-thienyl)-9H-pyrido [3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 67 and 68
(1S,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate
and
(1R,3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 69
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 70
(R)-N$^{\alpha}$-(3,4-Methylenedioxyphenylcarbonyl)-tryptophan methyl ester

Intermediate 71
(R)-N$^{\alpha}$-(3,4-Methylenedioxyphenylthiocarbonyl)-tryptophan methyl ester

Intermediate 72
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 73
(1R,3R)-Methyl 1,2,3,4-tetrahydro-2-chloroacetyl-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 74
Methyl 1,2,3,4-tetrahydro-6-methyl-1-(3,4-methylene-dioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis and trans isomers

Intermediates 75 and 76
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-Methyl 1,2,3,4-tetrahydro-1-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]-oxazinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediate 77
Methyl 1,2,3,4-tetrahydro-1-(5-(N-benzylindolinyl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R, 3R) and (1S, 3R) isomers

Intermediates 78 and 79
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(4-carbomethoxy-phenyl)-9H-pyrido[3,4-b]indole-3-carboxylate, trans isomer

Intermediate 80
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxy-carbonyl)-R-prolyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 81
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-[2-(benzyloxy-carbonyl)-S-prolyl]-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 82
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloro-propionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4-b]indole-3-carboxylate

Intermediate 83
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-2-(2-chloro-propionyl)-1-(3,4-methylenedioxyphenyl)-9H-pyrido-[3,4-b]indole-3-carboxylate

Intermediates 84 and 85
(1R, 3R)-Methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzyl-oxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylate cis isomer and (1S, 3R)-methyl 1,2,3,4-tetrahydro-1-(3,4-dibenzyloxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate trans isomer

Intermediate 86
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dibenzyl-oxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione

Intermediate 87
Methyl 1,2,3,4-tetrahydro-1-(5-(2-methylisoindol-inyl))-9H-pyrido[3,4-b]indole-3-carboxylate, mixture of (1R,3R) and (1S,3R) isomers

Intermediates 88 and 89
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-9H-pyrido[3,4-b]indole-3-carboxylate, cis isomer and
(1S,3R)-methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-9H-pyrido[3,4-b]indole-3-carboxylate trans isomer

Intermediate 90
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-chloroacetyl-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 91
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-(2-(S)-benzyloxycarbonylaminopropionyl)-9H-pyrido[3,4-b]indole-3-carboxylate

Intermediate 92
(1R,3R)-Methyl 1,2,3,4-tetrahydro-1-(5-benzofuranyl)-2-[2-(S)-benzyloxycarbonylmethylamino)propionyl]-9H-pyrido-[3,4-b[indole-3-carboxylate

Example 1
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylene-dioxyphenyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from Intermediate 1 and methylamine.

The following compounds were obtained in a similar manner:

Example 2
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-10-fluoro-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from butylamine and Intermediate 52.

Example 3
Trans-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methyl-enedioxyphenyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from methylamine and Intermediate 2.

Example 4
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ammonia and Intermediate 1.

Example 5
Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-6-(4-methoxy-phenyl)-2-(2,2,2-trifluoroethyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from 2,2,2-trifluoroethylamine and Intermediate 52.

Example 6
Cis-2,3,6,7,12,12a-hexahydro-10-fluoro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 50.

Example 7
(6R, 12aS)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6.1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the trans isomer of Intermediate 56.

Example 8
(6S, 12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino [2',1':6.1]pyrido-[3,4-b]indole-1,4-dione--from methylamine and Intermediate 55.

Example 9
Cis-2, 3, 6, 7, 12, 12a-hexahydro-2-[2-(2-pyridyl)-ethyl]-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1'-6,1]pyrido[3,4-b]indole-1,4-dione--from 2-(2-pyridyl)ethylamine and Intermediate 1.

Example 10
Cis-2,3,6,7,12,12a-hexahydro-2-(2-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from 2-pyridylmethyl-amine and Intermediate 1.

Example 11
Cis-2,3,6,7,12,12a-hexahydro-2-(3-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from 3-pyridylmethyl-amine and Intermediate 1.

Example 12
Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from 4-pyridylmethyl-amine and Intermediate 1.

Example 13
Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(3,4-methyl-enedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole -1,4-dione--from ethylamine and Intermediate 1.

Example 14
Cis-2,3,6,7,12,12a-hexahydro-2-(2,2,2-trifluoro-ethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from 2,2,2-trifluoroethylamine and Intermediate 1.

Example 15
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-methylenedioxy-phenyl)-2-propyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from propylamine and Interme-diate 1.

Example 16
Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from isopropylamine and Inter-mediate 1.

Example 17
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylamine and Intermediate 1.

Example 18
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 1.

Example 19
Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 2.

Example 20
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-methylamine and Intermediate 1.

Example 21
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 1.

Example 22
Cis-2,3,6,7,12,12a-hexahydro-2-cyclohexyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclohexylamine and Intermediate 1.

Example 23
Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and Intermediate 1.

Example 24
Cis-2,3,6,7,12,12a-hexahydro-2-(4-fluorobenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from 4-fluorobenzylamine and Intermediate 1.

Example 25
Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 3.

Example 26
Trans-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 4.

Example 27
Cis-2,3,6,7,12,12a-hexahydro-2-ethyl-6-(4-methoxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ethylamine and Intermediate 3.

Example 28
Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-(2,2,2-trifluoroethyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from 2,2,2-trifluoro-ethylamine and Intermediate 3.

Example 29
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 3.

Example 30
Trans-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methoxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 4.

Example 31
Cis-2,3,6,7,12,12a-hexahydro-6-(4-methoxyphenyl)-2-cyclopropylmethylpyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from cyclopropylmethylamine and Intermediate 3.

Example 32
Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-(4-methoxy-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and Intermediate 3.

Example 33
Cis-2,3,6,7,12,12a-hexahydro-6-(3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 5.

Example 34
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 6.

Example 35
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethoxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 6.

Example 36
Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]-furan-5-yl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 8.

Example 37
Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo[b]-furan-5-yl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-methylamine and Intermediate 8.

Example 38
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxy-phenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from methylamine and Intermediate 10.

Example 39
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-ethylenedioxyphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 10.

Example 40
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 12.

Example 41
Cis-2,3,6,7,12,12a-hexahydro-6-(4-chlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 13.

Example 42
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-chlorophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 13.

Example 43
Cis-2,3,6,7,12,12a-hexahydro-6-(3,4-dichlorophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 15.

Example 44
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and cis-methyl 1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate.

Example 45
Cis-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate.

Example 46
Trans-2,3,6,7,12,12a-hexahydro-2-benzyl-6-phenyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from benzylamine and cis-methyl-1,2,3,4-tetrahydro-1-phenyl-9H-pyrido[3,4-b]indole-3-carboxylate.

Example 47
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from methylamine and Intermediate 17.

Example 48
Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(1,2,3,4-tetrahydro-6-naphthyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from isopropylamine and Intermediate 17.

Example 49
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(1,2,3,4-tetrahydro-6-naphthyl))-pyrazino[2',1':-6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropyl-methylamine and Intermediate 17.

Example 50
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(2-naphthyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 18.

Example 51
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 20.

Example 52
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 24.

Example 53
Cis-2,3,6,7,12,12a-hexahydro-6-(4-bromo-2-thienyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 26.

Example 54
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 24.

Example 55
Cis-2,3,6,7,12,12a-hexahydro-6-(5-bromo-2-thienyl)-2-cyclopentyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 24.

Example 56
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of Intermediate 66.

Example 57
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 22.

Example 58
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(3-thienyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 22.

Example 59
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of Intermediate 28.

Example 60
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(5-methyl-2-furyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 29.

Example 61
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-methyl-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 31.

Example 62
Cis-2,3,6,7,12,12a-hexahydro-2-isopropyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from isopropylamine and Intermediate 31.

Example 63
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methyl-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 31.

Example 64
Cis-2,3,6,7,12,12a-hexahydro-2-cyclopropylmethyl-6-(4-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from cyclopropylmethylamine and Intermediate 31.

Example 65
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-methyl-phenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 33.

Example 66
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-trifluoro-methylphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from butylamine and Intermediate 35.

Example 67
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-tri-fluoromethoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of Intermediate 65.

Example 68
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(4-hydroxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 39.

Example 69
Cis-2,3,6,7,12,12a-hexahydro-6-(3-hydroxy-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 40.

Example 70
Cis-2,3,6,7,12,12a-hexahydro-6-(4-hydroxy-3-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 41.

Example 71
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-cyanophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 37.

Example 72
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from isopropylamine and the cis isomer of Intermediate 42.

Example 73
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and the cis isomer of Intermediate 42.

Example 74
Cis-2,3,6,7,12,12a-hexahydro-6-(4-isopropylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 43.

Example 75
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-nitrophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 45.

Example 76
Cis-2,3,6,7,12,12a-hexahydro-6-(4-dimethylaminophenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and the cis isomer of Intermediate 47.

Example 77
Cis-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3-pyridyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 48.

Example 78
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--Intermediate 54 and methylamine.

The following compounds were obtained in a similar manner:

Example 79
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from isopropylamine and Intermediate 54.

Example 80
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from butylamine and Intermediate 54.

Example 81
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isobutyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from isobutylamine and Intermediate 54.

Example 82
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 54.

Example 83
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-cyclohexylmethyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclohexylmethylamine and the cis isomer of Intermediate 56.

Example 84
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopropylmethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 57.

Example 85
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-butyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from butylamine and Intermediate 57.

Example 86
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--rom cyclopentylamine and Intermediate 57.

Example 87
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-cyclopropylmethyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 59.

Example 88
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-cyclopentyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from cyclopentylamine and Intermediate 59.

Example 89
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3-chloro-4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from methylamine and Intermediate 59.

Example 90
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-isopropyl-6-(3-chloro-4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido-[3,4-b]indole-1,4-dione--from isopropylamine and Intermediate 59.

Example 91
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydro-benzo[b]furan-5-yl)-2-methyl-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 61.

Example 92
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(2,3-dihydro-benzo[b]furan-5-yl)-2-methylcyclopropyl-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylcyclopropylamine and Intermediate 61.

Example 93
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from methylamine and Intermediate 63.

Example 94
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indanyl)-2-cyclopropylmethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from cyclopropylmethylamine and Intermediate 63.

Example 95
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 73 and methylamine.

Example 96
Cis-2,3,6,7,12,12a-hexahydro-2,10-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure used to prepare Example 1, but starting from methylamine and the cis isomer of Intermediate 74.

Example 97
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as used to prepare Example 78, but starting from veratrylamine and Intermediate 54.

Example 98
Cis-2,3,6,7,12,12a-hexahydro-6-(4-aminophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Example 75.

Example 99
Cis-2,3,6,7,12,12a-hexahydro-6-(4-acetamidophenyl)-2-butyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Example 98.

Example 100
Cis-2,3,6,7,12,12a-hexahydro-2-butyl-6-(4-methylsulfonamidophenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Example 98.

Example 101
(6R, 12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from the same procedure as Example 100 starting from ammonia and Intermediate 54.

Example 102
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-(2-propynyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from propargylamine and Intermediate 54.

Example 103
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-methylenedioxybenzyl)-6-(3,4-methylenedioxyphenyl)-pyrazino-[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from piperonylamine and Intermediate 54.

Example 104
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-(3,4-dimethoxyphenethyl)-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 3,4-dimethoxyphenethylamine and Intermediate 54.

Example 105
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-furfuryl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from furfurylamine and Intermediate 54.

Example 106
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-methylenedioxyphenyl)-2-(2-thienylmethyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from 2-thiophenemethylamine and Intermediate 54.

Example 107
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-methoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from methylamine and Intermediate 57.

Example 108
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-ethyl-6-(4-methoxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from the same procedure as Example 100 starting from ethylamine and Intermediate 57.

Example 109
(6R,12aR)-2,3,6,7,12,12a-hexahydro-6-(7-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazinyl))-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from Intermediate 75.

Example 110
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-(N-benzyl-indolinyl))-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from Intermediate 77.

Example 111
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-indolinyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Example 110.

Example 112
Cis-2,3,6,7,12,12a-hexahydro-6-(4-ethylphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from methylamine and the cis isomer of Intermediate 42.

Example 113
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(4-carbomethoxyphenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from the same procedure as Example 100 starting from Intermediate 78 (cis isomer) and methylamine.

Example 114
(5aR,12R,14aR)-1,2,3,5a,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1'',2'':4',5']-pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione--from Intermediate 80.

Example 115
(5aR,12R,14aS)-1,2,3,5,6,11,12,14a-Octahydro-12-(3,4-methylenedioxyphenyl)-pyrrolo[1'',2'':4',5']-pyrazino[2',1':6,1]pyrido[3,4-b]indole-5-1,4-dione--from Intermediate 81.

Example 116
(3R,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from Intermediate 82 and methylamine.

Example 117
(3S,6R,12aR)-2,3,6,7,12,12a-hexahydro-2,3-dimethyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from Intermediate 83 and methylamine.

Example 118
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(3,4-dihydroxy-phenyl)-2-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]-indole-1,4-dione--from Intermediate 86.

Example 119
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(5-(2-methylisoindolinyl))pyrazino[2',1':6,1]pyrido[3,4b]indole-1,4-dione--from Intermediate 87 and methylamine.

Example 120
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-methyl-pyrazino[2'1':6,1]pyrido[3,4-b]-indole-1,4-dione--and Intermediate 91 and methylamine.

Example 121
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from ammonia and Intermediate 91.

Example 122
(6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-2-isopropyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 91.

Example 123
(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(5-benzofuranyl)-3-methyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 92.

Example 124
(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-6-(t-benzofuranyl)-2,3-dimethyl-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione--from Intermediate 93.

Example 125
(3S,6R,12aR)-2,3,6,7,12,12a-Hexahydro-3-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione--from Intermediate 43 and ammonia.

TABLETS FOR ORAL ADMINISTRATION

A. Direct Compression

1.	mg/tablet
Active Ingredient	50.0
Crospovidone USNF	8.0
Magnesium Stearate Ph Eur	1.0
Anhydrous Lactose	141.0

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

2.	mg/tablet
Active Ingredient	50.0
Colloidal Silicon Dioxide	0.5
Crospovidone	8.0
Sodium Lauryl Sulfate	1.0
Magnesium Stearate Ph Eur	1.0
Microcrystalline Cellulose USNF	139.5

The active ingredient was sieved and blended with the excipients. The resultant mix was compressed into tablets.

B. Wet Granulation

1.	mg/tablet
Active ingredient	50.0
Polyvinylpyrrolidone	150.0
Polyethylene glycol	50.0
Polysorbate 80	10.0
Magnesium Stearate Ph Eur	2.5
Croscarmellose Sodium	25.0
Colloidal Silicon Dioxide	2.5
Microcrystalline Cellulose USNF	210.0

The polyvinylpyrrolidone, polyethylene glycol, and polysorbate 80 were dissolved in water. The resultant solution was used to granulate the active ingredient. After drying, the granules were screened then extruded at elevated temperatures and pressures. The extrudate was milled and/or screened, then was blended with the microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The resultant mix was compressed into tablets.

2.	mg/tablet
Active Ingredient	50.0
Polysorbate 80	3.0
Lactose Ph Eur	178.0
Starch BP	45.0
Pregelatinized Maize Starch BP	22.5
Magnesium Stearate BP	1.5

The active ingredient was sieved and blended with the lactose, starch, and pregelatinized maize starch. The polysorbate 80 was dissolved in purified water. Suitable volumes of the polysorbate 80 solution were added and the powders were granulated. After drying, the granules were screened and blended with the magnesium stearate. The granules were then compressed into tablets.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to the other excipients.

FILM COATED TABLETS

The aforementioned tablet formulations were film coated.

Coating Suspension	% w/w
Opadry white †	13.2
Purified water Ph Eur	to 100.0*

* The water did not appear in the final product. The maximum theoretical weight of solids applied during coating was 20 mg/tablet.

† Opadry white is a proprietary material obtainable from Colorcon Limited, UK, which contains hydroxypropyl methylcellulose, titanium dioxide, and triacetin.

The tablets were film coated using the coating suspension in conventional film coating equipment.

CAPSULES

1.	mg/capsule
Active Ingredient	50.0
Lactose	148.5
Polyvinylpyrrolidone	100.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

2.	mg/capsule
Active Ingredient	50.0
Microcrystalline Cellulose	233.5
Sodium Lauryl Sulfate	3.0
Crospovidone	12.0
Magnesium Stearate	1.5

The active ingredient was sieved and blended with the excipients. The mix was filled into size No. 1 hard gelatin capsules using suitable equipment.

Other doses can be prepared by altering the ratio of active ingredient to excipient, the fill weight, and, if necessary, changing the capsule size.

3.	mg/capsule
Active Ingredient	50.0
Labrafil M1944CS	to 1.0 ml

The active ingredient was sieved and blended with the Labrafil. The suspension was filled into soft gelatin capsules using appropriate equipment.

Inhibitory Effect on cGMP-PDE

cGMP-PDE activity of compounds of the present invention was measured using a one-step assay adapted from Wells et al., *Biochim. Biophys.*

Acta, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 μg/ml 5'-Nucleotidase, 1 mM EGTA, and 0.15 μM 8-[H^3]-cGMP. The enzyme used was a human recombinant PDE5 (ICOS Corp., Bothell, Washington).

Compounds of the invention were dissolved in DMSO finally present at 2% in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30%.

The IC_{50} values for the compounds examined were determined from concentration-response curves typically using concentrations ranging from 10 nM to 10 μM. Tests against other PDE enzymes using standard methodology also showed that compounds of the invention are highly selective for the cGMP-specific PDE enzyme.

cGMP Level Measurements

Rat aortic smooth muscle cells (RSMC), prepared according to Chamley et al., *Cell Tissue Res.*, *177*, 503-522 (1977), were used between the 10th and 25th passage at confluence in 24-well culture dishes. Culture media was aspirated and replaced with PBS (0.5 ml) containing the compound tested at the appropriate concentration. After 30 minutes at 37°C, particulates guanylate cyclase was stimulated by addition of ANF (100 nM) for 10 minutes. At the end of incubation, the medium was withdrawn, and two extractions were performed by addition of 65% ethanol (0.25 ml). The two ethanolic extracts were pooled and evaporated until dryness, using a Speed-vac system. cGMP was measured

after acetylation by scintillation proximity immunoassay (AMERSHAM). The EC_{50} values are expressed as the dose-giving half of the stimulation at saturating concentrations.

Biological Data

The compounds according to the present invention were typically found to exhibit an IC_{50} value of less than 500 nM and an EC_{50} value of less than 5 μM. *In vitro* test data for representative compounds of the invention is given in the following table:

Table 1: *In vitro* Results		
Example No.	IC_{50} (nM)	EC_{50} (μM)
12	10	0.15
36	<10	0.5
52	20	0.8
63	30	0.35
78	2	0.2
79	<10	0.15
82	20	0.5
84	10	0.4
89	10	<0.1
95	2	0.2
101	10	0.3
115	<10	0.4
117	2	0.2
120	15	0.6
121	20	<1
122	30	<1
123	8	<1
124	8	<1

The hypotensive effects of compounds according to the invention as identified in Table 2 were studied in conscious spontaneously hypertensive rats (SHRs). The compounds were administered orally at a dose of 5 mg/kg in a mixture of 5% DMF and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for five hours after administration. The results

are expressed as Area Under the Curve (AUC) from 0 to 5 hours, mm Hg•hours of the fall in blood pressure over time.

Table 2. *In vivo* results

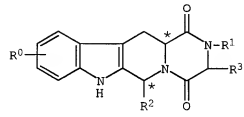
Example No.	SHR AUC PO (mm Hg.h)
36	99
63	95
79	171
82	111
84	77
89	117
95	135
101	136
120	137
121	93
122	108
123	101
124	89

Obviously, many modifications and variations of the invention as hereinbefore set forth can be made without departing from the spirit and scope thereof, and, therefore, only such limitations should be imposed as are indicated by the appended claims.

WHAT IS CLAIMED IS:

1. A combination comprising:

(a) a compound represented by a formula (I)



(I)

and salts and solvates thereof, in which:

R^0 represents hydrogen, halogen or C_{1-6}-alkyl;

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-6}-alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-3}alkyl, arylC_{1-3}alkyl, or heteroaryl-C_{1-3}alkyl;

R^2 represents an optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine or an optionally substituted bicyclic ring

attached to the rest of the molecule via one of the benzene ring carbon atoms and wherein the fused ring

A is a 5- or 6-membered ring which may be saturated or partially or fully unsaturated and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulphur and nitrogen; and

R^3 represents hydrogen or C_{1-3}alkyl, or R^1 and R^3 together represent a 3- or 4- membered alkyl or alkenyl chain; and

(b) a second therapeutically active agent,

for simultaneous, separate, or sequential use in the treatment of condition where inhibition of a cGMP-specific PDE is of a therapeutic benefit.

2. A pharmaceutical formulation comprising a combination according to claim 1, together with a pharmaceutically acceptable diluent or carrier.

3. The combination of claim 1 wherein the condition is stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, a peripheral vascular disease, a vascular disorder, Raynaud's disease, thrombocythemia, an inflammatory disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, osteoporosis, preterm labor, benign prostatic hypertrophy, a gut motility disorder, or irritable bowel syndrome.

4. The combination of claim 1 wherein the condition is erectile dysfunction in a male or female animal.

5. The combination of claim 1 wherein the second therapeutically active agent comprises a vasodilator, prostaglandin E1, prostacyclin, an α-adrenergic blocker, a mixed α,β-blocker, an α_2-adrenergic blocker, an ACE inhibitor, an NEP inhibitor, a centrally acting dopaminergic agent, a vasoactive intestinal peptide, a calcium channel blocker, a thiazide, or a mixture thereof.

6. The combination of claim 5 wherein the vasodilator is selected from the group consisting of an organic nitrate, an organic nitrite, a thionitrite, a thionitrate, an S-nitrosothiol, a nitrosoprotein, a substituted furoxane, a substituted sydnonimine, a nitrosyl complex compound, nitric oxide, or a mixture thereof.

7. The combination of claim 5 wherein the vasodilator is selected from the group consisting of nitroglycerin, isosorbide dinitrate, pentaerythrityl tetranitrate, isosorbide-5-mononitrate, propatyl nitrate, trolnitrate, nicroandil, mannitol hexanitrate, inositol hexanitrate, N-[3-nitratopivaloyl]-6-cysteine ethyl ester, isoamyl nitrite, S-nitroso-N-acetyl-D,L-penicillamine, 1,2,5-oxadiazole-2-oxide, furazan-N-oxide, molsidomine, mesocarb, an iron nitrosyl compound, sodium nitroprusside, nitric oxide, and mixtures thereof.

8. The combination of claim 1 wherein the second therapeutially active compound is selected from the group consisting of prostaglandin E1, prostocyclin, apomorphine, yohimbine, phentolamine, prazocin, carvedilol, and mixtures thereof.

9. A method of treating a condition where inhibition of a cGMP-specific PDE is of therapeutic benefit, in a human or a nonhuman animal body, comprising administering to said body a therapeutically effective amount of a combination of claim 1.

10. The method of claim 9 wherein the cGMP-specific PDE is PDE5.

11. The method of claim 9 comprising a prophylactic or curative treatment of erectile dysfunction in a male or female animal.

12. The method of claim 1 wherein the male or female animal is a human male or female animal.

13. The method of claim 9 wherein the treatment is an oral treatment.

14. A method of treating stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, glaucoma, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, or irritable bowel syndrome, in a human or nonhuman animal body, said method comprising administering to said body a therapeutically effective amount of a combination of claim 1.

15. The method of claim 14 wherein the combination is administered orally.

INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 99/19466

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4985 A61P9/08 A61P15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 96 38131 A (GLAXO GROUP LTD.) 5 December 1996 (1996-12-05) page 1, line 3 - line 13 page 4, line 10 - line 35 page 7, line 23 -page 9, line 7 page 11, line 11 - line 28 claims 1,5,15,23-26,33,34 ---	1-13
X,Y	WO 97 03675 A (LABORATOIRE GLAXO WELLCOME S.A.) 6 February 1997 (1997-02-06) cited in the application page 1, line 3 -page 6, line 28 page 12, line 15 -page 17, line 27 claims 1-12 --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 December 1999	10/12/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Economou, D

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